in 16% of LZ patients vs. 7% of controls. Forty-six percent of LZ patients vs. 13% of controls failed to achieve platelet engraftment. The cumulative incidence of engraftment of neutrophils plus platelets (using death without engraftment as the competing risk) was lower in the LZ group (54%) vs. the control group (83%) ($P = .005$). Day 100 survival rates were 58% for the LZ group vs. 92% for controls. Survival probability is shown in Figure 1.

Conclusions: LZ does not significantly affect time to neutrophil engraftment, but does appear to prolong time to platelet engraftment when compared to patients who did not receive LZ. LZ should be used cautiously early after stem cell transplantation.

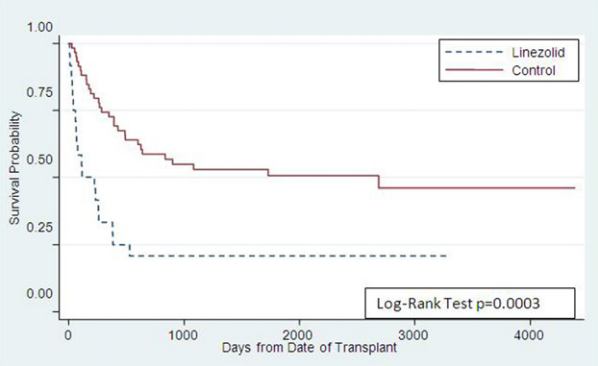

Figure 1. Overall Survival

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Association Between Mycophenolic Acid (MPA) Total Serum Trough Levels and Toxicity and Efficacy Outcomes in Cord Blood Transplantation (CBT) Recipients

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Background: Mycophenolate mofetil (MMF) is frequently combined with cyclosporine-A as immunosuppression in unrelated donor CBT. Recent evidence suggests that therapeutic drug monitoring of mycophenolic acid (MPA), the active metabolite of MMF, is advisable based on intra- and inter-patient variability of MMF pharmacokinetics (PK). Moreover, an increased incidence of acute graft-versus-host disease (aGVHD) has been associated with low unbound MPA AUCs in adult allograft recipients. This is highly relevant in CBT as aGVHD is a leading cause of transplant-related mortality. However, as AUCs are cumbersome, a limited PK parameter such as MPA troughs would be ideal. Also, the toxicity associated with MPA trough levels is not established.

Methods: We evaluated the association between serial MPA total serum trough levels in weeks 1-6 and transplant outcomes in pediatric and adult double-unit CB recipients transplanted 8/2009 to 6/2012 for hematologic malignancies with 4-6/6 HLA-A,B antigen, DRB1 allele matched CB grafts. To evaluate the association between trough levels and outcomes, the trough levels were dichotomized into < 2 mcg/mL and ≥ 2 mcg/mL for toxicity (delayed engraftment, gastrointestinal toxicity, viral infection), and < 0.5 mcg/mL and ≥ 0.5 mcg/mL for efficacy (aGVHD prevention) at each time point.

Results: Seventy-four patients had MPA total serum trough levels drawn weekly for 6 weeks. Sixty-one (82%) received myeloablative (MA) conditioning and 31 (42%) were CMV seropositive. Median trough levels by week were 0.9, 0.9, 0.6, 0.7, 0.9, and 1.3 mcg/mL. The change in trough levels over time did not reach significance ($P = .07$). Recipients of MA conditioning had lower MPA troughs than those who received non-myeloablative conditioning ($P = .03$). By time-dependent Cox regression analysis, there was no association between trough levels and toxicity as measured by time to neutrophil and platelet recovery or duration of total parenteral nutrition (TPN) in myeloablative CBT recipients, or time to viremia in CMV seropositive patients (Table 1A). In a competing risk 2-week landmark analysis, while differences between groups did not reach significance, it was notable that the incidence of severe (grade III-IV) aGVHD was more than doubled in those with a mean week 1 and 2 trough level < 0.5 mcg/mL (Table 1B).

Conclusions: Analysis of this limited patient population suggests that while MPA total serum trough levels appear to have little effect on toxicity outcomes, the early post-transplant (week 1-2) mean levels could be associated with the risk of severe (grade III-IV) aGVHD. Further investigation in a larger patient series is warranted.

Table
Association between MPA total serum trough levels and toxicity and efficacy outcomes

1A) Toxicity outcome: Time-dependent Cox regression

Outcome	N	HR (95% CI)	*P*-value
Time to neutrophils ≥ 0.5 k/mcL	61	1.45 (0.65 - 3.25)	0.36
Time to platelets ≥ 20 k/mcL	61	1.88 (0.82 - 4.30)	0.14
Time to TPN cessation	61	0.56 (0.20 - 1.58)	0.28
Time to CMV viremia	31	1.71 (0.38 - 7.59)	0.48

IB) Efficacy outcome: Cumulative incidence of aGVHD by day 100

Outcome	N	Cumulative incidence (95% CI)	*P*-value
aGVHD II-IV			
Trough < 0.5 mcg/mL	15	0.67 (0.41 - 0.92)	0.29
Trough ≥ 0.5 mcg/mL	57	0.57(0.44 - 0.71)	
aGVHD III-IV			
Trough < 0.5 mcg/mL	15	0.27 (0.03 - 0.50)	0.12
Trough < 0.5 mcg/mL	57	0.11 (0.03 - 0.19)	

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Incidence of Fluoride Toxicity in Allogeneic Hematopoietic Stem Cell Transplant (HSCT) Patients Taking Voriconazole

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Background: Guidelines recommend anti-mold prophylaxis in HSCT patients deemed high-risk for IFI; this has led to long-term use of voriconazole following allogeneic HSCT in patients that remain immunocompromised. Voriconazole has three fluoride atoms and has been associated with periostitis, exostoses, and fluoride toxicity in patients taking voriconazole following solid organ transplant, HSCT and leukemia therapy.
Objectives: To describe the incidence of fluoride toxicity in allogeneic HSCT patients taking voriconazole that had a fluoride level measured, identify when a fluoride level was measured due to symptomatic fluoride toxicity in relation to voriconazole initiation, and describe the clinical presentation and outcomes of patients with fluoride toxicity in HSCT patients.
Methods: Retrospective review of all adult allogeneic HSCT patients at Mayo Clinic Rochester between 1/1/09 – 7/31/12. Fluoride assays were conducted with an ion selective electrode (normal range 0 – 4 μmol/L).
Results: 292 patients received an allogeneic HSCT between 1/1/09 – 7/31/12. Patients were excluded if they did not consent to research (n=4), were treated by the pediatric service (n=7), or did not receive voriconazole for more than 7 days (n=38). The median duration of voriconazole was 167 days (range 7–1321). Of 243 patients included, 32 presented with musculoskeletal pain and had a fluoride assay. In 31 patients with fluoride measured while on voriconazole, 29 (93.5%) had elevated fluoride levels; 1 patient had a normal fluoride level measured 1 month after voriconazole discontinuation due to pain. The median fluoride level was 10.5 μmol/L (range 2-24.7). The median time to measurement of fluoride was 113 days following voriconazole initiation (range 28 – 692). Of the 29 patients with an elevated fluoride level, pain improved in 17 patients following voriconazole discontinuation; 2 patients did not have improvement after holding voriconazole for 1 week and resumed voriconazole. Four patients had repeat fluoride measurement and subsequently discontinued voriconazole because of pain; pain improved in 2 of those patients, did not improve in 1 patient and 1 patient was not assessed. Six patients continued voriconazole; pain resolved in 4 of those patients, was not assessed in 1 patient and persisted in 1 patient with recurrent leukemia. Eight patients (27.6%) with elevated fluoride levels had an estimated glomerular filtration rate < 50 mL/min.
Conclusions: Of 243 consecutive allogeneic HSCT patients receiving voriconazole for more than 7 days, the development of musculoskeletal pain in 32 (13.2%) patients led to fluoride assessment; 29 patients (93.5%) with fluoride levels measured while on voriconazole had elevated levels. Fluoride toxicity is an adverse effect of voriconazole that should be considered in patients presenting with pain and is often reversible following drug discontinuation.

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Efficacy of Low-Dose Acyclovir Prophylaxis Against Varicella Zoster Virus in Pediatric Hematopoietic Stem Cell Transplantation Patients

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Background: Prophylaxis with low-dose acyclovir is effective in lowering the incidence of Varicella zoster virus (VZV) reactivation and infections during the first year post-transplant in adult hematopoietic stem cell transplantation (HSCT) patients. Such data are lacking in the pediatric population. The objective of this study was to determine the effectiveness of low-dose acyclovir prophylaxis in preventing VZV reactivations and infections in the pediatric HSCT patients.

Methods Medical records of VZV seropositive patients, < 18 years of age who received a HSCT between January 2000 and April 2010 were retrospectively reviewed for: demographics, pre-transplant serology for herpes simplex virus, VZV and cytomegalovirus, acyclovir (ACV) dosing both intravenous (IV) and oral (PO), duration of acyclovir prophylaxis, incidence of reactivation, time to reactivation, age at reactivation, acyclovir prophylaxis status at the time of reactivation, severity of zoster infection, duration of follow-up, graft versus host disease (GVHD) prophylaxis, incidence of GVHD, treatment of acute or chronic GVHD, deaths, cause of death, and any adverse effects attributed to acyclovir. Data was analyzed using descriptive statistics.
Results:

Table

Demographics	
N	88
Age in years (range)	6 ± 5.8* (0.67-18)
Male	63%
Donor Source	
Bone Marrow	44
Peripheral Stem Cells	43
Umbilical Cord Blood	1
Stem Cell Dose (CD34 x106/kg body weight)	7.94 ± 6.45* (0.85-33)
Type of Transplantation	
Autologous	32
Allogeneic	56
GVHD Prophylaxis	
Cyclosporine and Methotrexate	32
Tacrolimus and Methotrexate	9
Other	11
OUTCOMES	
PO ACV in mg/kg/dose (range)	9.8 ± 3.5* (2.4-28)
PO ACV in mg/dose (range)	200 ± 105* (100-400)
Duration of PO ACV in days (range)	345 ± 154*(7-1337)
Number of VZV Reactivations	1
Time from Transplantation to VZV Reactivation (range)	498 days
Deaths	3 (relapsed) 1 (cardiac arrest)
Deaths due to VZV	0

Conclusion: ACV at a median dose of 20 mg/kg/day twice daily was successful in preventing reactivations of VZV in 99 % of pediatric HSCT patients. The median duration of oral ACV prophylaxis in these patients was 345 days. Reactivation was detected by a qualitative polymerase chain reaction test positive for the viral DNA in a superficial tissue sample. Repeat test conducted three weeks later was negative. The patient was not on ACV at the time of reactivation, did not require treatment for VZV infection, but was started on valacylovir prophylaxis. According to the guidelines for preventing infectious complications among HSCT recipients, the recommended oral ACV dose for VZV prophylaxis is 60-80 mg/kg/day in two to three divided doses for children <40 kg body weight and 800 mg of oral ACV twice daily for children >40 kg body weight. At a dose